

Pandemic Influenza Issues

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Video Communications Division

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Objectives

- Introduce pandemic influenza issues.
- Explain Alabama's sentinel influenza system.
- Relate mass vaccination exercises to pandemic influenza.
- Describe the risk of Avian and other animal influenza.
- Explain the difference between antigenic drift and antigenic shift.
- Learn how influenza disease spreads across species.

Avian Influenza As A Zoonotic Agent

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Influenza Background

- The normal host and reservoir for type A influenza viruses are wild waterfowl, shorebirds, and gulls.
- Infection in the natural host is generally subclinical.
- All type A influenza viruses in domestic animals and humans are thought to originate from a wild bird source.

Influenza Background

- Type B and C influenza viruses are human viruses that may cross over to other species (swine, seals).
- Poultry, including chickens and turkeys, are abnormal hosts for Avian Influenza viruses.

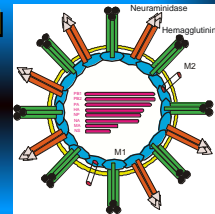
Isolation of Avian Influenza from Different Wild Bird Species

- Most isolations from Anseriformes (ducks, geese, and swans) and Charadriiformes (gulls, terns, plovers, surfbirds, sandpipers, puffins).
- Within Anseriformes most isolations from Mallards and other dabbling ducks.

Isolation of Avian Influenza from Different Wild Bird Species

- Isolations of virus from many other orders of birds (ex. loons, grebes, shearwaters, pelicans, herons, and coots).
- The complete host range is not known.

Influenza A Virus Negative sense RNA Single Stranded Segmented



15 Hemagglutinin subtypes
9 Neuraminidase subtypes

Hemagglutinin (HA) Protein

- Surface glycoprotein that must be cleaved into HA1 and HA2 subunits to be infectious (necessary to release fusion domain).
- HA contains receptor binding site (receptor = sialic acid).
- Fusion domain becomes active when pH is lowered in endosome.
- Antibodies to HA are the most important for protective immunity.
- No cross protection between HA subtypes (15).

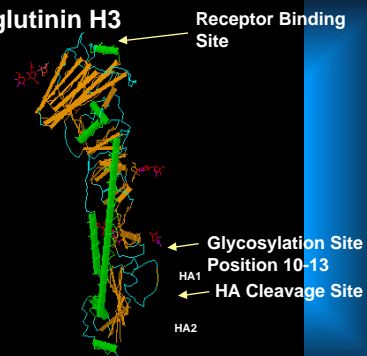
Sialic Acid As A Receptor

- Sialic acid is one type of sugar found in glycosylated proteins.
- Sialic acid can be attached to the galactose backbone by different linkages.
- 2,3 and 2,6 are the most common with some animals having primarily one or both of these linkages.

Sialic Acid As A Receptor

- Influenza viruses have preferences for one type of linkage, with most Avian viruses having an α 2,3 preference and human viruses having an α 2,6 linkage.
- Most birds have α 2,3 sialic acid, humans α 2,6 and swine both α 2,3 and α 2,6.

Hemagglutinin H3

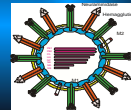


Reassortment of Gene Segments

- Influenza has 8 separate gene segments that encode at least 10 different proteins
- When a host cell is infected with two different influenza viruses, the progeny virus can be a mixture of both "parent" viruses

Reassortment of Gene Segments

- Reassortment provides for increased biological variation that increases the ability of the virus to adapt to new hosts
- This process may be thought of as sex for viruses



Influenza: Infection and Disease

- Infection can be asymptomatic or cause severe disease with high mortality.
- Localized vs. systemic infection.
- Enteric-wild ducks and shorebirds, poultry.
- Respiratory-humans, swine, horses, poultry, domestic ducks, seal, mink.
- Systemic-chickens, turkeys, other gallinaceous birds, terns

Protection from Clinical Disease

- Antibody to the hemagglutinin protein provides primary protection from clinical disease.
- Neuraminidase protein can be protective, but current vaccines don't produce high levels of antibody to neuraminidase.
- Antibody to internal proteins are not protective.

Protection from Clinical Disease

- Cell mediated immunity may provide some protection.
- Vaccination and even prior infection protects from clinical disease not from infection.

Antigenic Drift

- Antigenic drift - accumulation of point mutations in influenza viral genes (HA) that result in decreasing antibody protection.
- Current vaccines must be reevaluated yearly to assure a good antigenic match of vaccine to likely challenge strain.
- An educated guess is used to predict what the circulating strain will be for the following year to give time to produce the vaccine.

Antigenic Shift

- Antigenic shift- circulation of an influenza virus with a HA subtype that is new to the host population.
- Host population has no or only limited protection to the new virus.
- Occurs only in longer lived animals that are naturally exposed or vaccinated (swine, horses, humans).
 - Spanish Flu H1N1 1917
 - Asian Flu H2N2 1957
 - Hong Kong Flu H3N2 1968
 - Equine Type 2 H3N8

Adaptation of AIV to New Host

- Wildbird AIVs are well adapted to natural host (internal genes are well conserved).
- Viruses can adapt to new host by both by mutation (ex., changes to receptor binding site) and reassortment (mixing of animal and human influenza genes).

Adaptation of AIV to New Host

- Viruses probably don't replicate or transmit well early in outbreak, but given the opportunity the viruses can adapt (species that congregate in large numbers at greater risk).
- Eventually viruses become more adapted to the new host species, and no longer replicate well in the originating wild bird host.

Requirements for Influenza to Become Endemic in New Host

- Efficient replication in host species.
 - Avian influenza experimentally has a wide host range.
 - Receptor binding (2,3 vs 2,6 linkage in sialic acid) plays a role.
 - Internal gene constellation critical for efficient replication.

Requirements for Influenza to Become Endemic in New Host

- Efficient transmission.
 - Many AI viruses replicate well in new host, but fail to transmit efficiently (ex., H5N1 in humans).
 - Factors affecting transmission unknown.

Influenza Host Specificity

- Some host specificity occurs in wild birds (ex., gull lineage).
- Endemic influenza in domestic animals and humans are generally host specific.
- Numerous exceptions have been documented where influenza viruses cross the species barrier and replicate in other hosts (swine flu in turkeys).

Influenza Host Specificity

- Both efficient replication and transmission however are required before an epidemic will occur.
- Rapid adaptation, by reassortment and mutation, allows viruses (rarely) to establish new host ranges.

Highly Pathogenic Avian Influenza

- Systemic, rapidly fatal disease of gallinaceous birds.
- Only H5 and H7 subtypes are recognized to cause HPAI, but not all H5 and H7 viruses are highly pathogenic.
- HA cleavage site critical virulence factor.
- Virulence in humans and birds not clearly associated.

Model 1 of Viral Spread

- Direct spread of Avian Influenza viruses from wild bird reservoir to new host.
 - Virus must replicate and transmit efficiently in new host to be maintained.
 - The constellation of all eight influenza genes are important.
 - Sialic present (2,3 and 2,6) in host may be an important factor.
 - Host genetics are important (turkey susceptibility>chickens).

Avian Influenza Viruses From Wild Birds(?) Crossing Mammalian Species Barrier

Species	Subtype	Location and Year
Striped Whales	H1N3	Pacific Ocean 1976
Swine	H3N2	China 1978-
Swine	H1N1	Europe and Asia 1979-
Seals, Humans	H7N7	Massachusetts 1980
Harbor Seals	H4N5	New England 1982-83
Pilot Whale	H13N9	Portland, Maine 1984
	H13N2	
Mink	H10N4	Sweden 1984
Equine	H3N8	Northeast China 1989
Seal	H3N3	New England 1991,1992
Seal	H4N6	New England 1991,1992
Human	H7N7	England 1996
Swine	H4N6	Canada 1999

Human H7N7 in England

- A single case of self-limiting conjunctivitis occurred in an adult female in 1996.
- H7N7 Avian-like influenza was isolated.
- Woman raised ducks and had history of foreign body (straw) in her eye.
- No spread of infection was observed.
- H7N7 has been associated with human disease on four different occasions.

Example of Avian Influenza in Swine

- In 1999 a disease outbreak of H4N6 influenza in swine farm in Ontario.
- Pigs were exposed to untreated lake water (likely exposure to AI virus).
- Evidence of limited spread of the virus to other swine herds.
- Outbreak was self-limiting.
- Outbreaks like that this may be common but undiagnosed.
- H9N2, H5N1, and other subtypes reported from Asia.

Experimental Infections in Mammals with Avian Influenza

- Cats, mice, pigs, squirrel monkeys, rhesus monkeys, and cynomolgus macaques have all been experimentally infected with Avian Influenza.

Experimental Infections in Mammals with Avian Influenza

- Mice are commonly used.
 - Typically influenza must be adapted to mice before clinical disease is observed.
 - Rarely (ex., H5N1 Asia viruses) will cause severe disease and death without prior adaptation.

Experimental Infections in Mammals with Avian Influenza

- Ferrets used routinely for human influenza.
- Cynomolgus macaques had similar disease to humans infected with H5N1 Avian Influenza.

Experimental Infections of AIV in Humans

"Replication of avian influenza viruses in humans"
Archives of Virology (1991) 119:37-42

- Nine different Avian Influenza viruses were experimentally inoculated into humans.
- Virus shedding, clinical disease, and antibody titers were monitored.

- Three viruses replicated in humans with virus shedding and mild clinical disease, but no rise in antibody titers.
 - Duck/Pennsylvania/486/69 (H6N1)
 - Duck/Alberta/288/78 (H4N8)
 - Turkey/Minnesota/3/79 (H10N7)
- Some volunteers had increased antibody titers to other subtypes but no detectable virus shedding (4 of 9 viruses).

Model 2 of Viral Spread

- Mixing vessel hypothesis.
 - Reassortment of two viruses in a susceptible host that broadens host range.
 - Swine have both 2,3 and 2,6 sialic acid linkages.
 - Avian viruses and human viruses can both potentially replicate in swine.

Model 2 of Viral Spread

- If both viruses infect a pig at the same time, they can potentially reassort, resulting in a virus with an Avian Influenza hemagglutinin gene with human adapted internal genes.
- Such a virus could theoretically replicate and transmit well in the new host (humans), resulting in an antigenic shift and a new human pandemic.

Evidence for Mixing Vessel

- Experimentally, many AI viruses will replicate in swine to reasonable high titers.
- Many examples of human viruses infecting swine and swine viruses infecting humans (occasionally with lethal results).
- Several examples of human-swine reassortant viruses being isolated from pigs.

Evidence for Mixing Vessel

- Currently human-swine-Avian reassortant viruses are circulating in U.S. swine population since 1999.
- At least one example of human-swine reassortant viruses infecting people.

Human Pandemics Caused By Antigenic Shifts

- An antigenic shift is predicted to occur every 20 years.
- In 1918, a H1N1 virus emerged with Avian-like genes resulted in Spanish flu (possible swine involvement?)

Human Pandemics Caused By Antigenic Shifts

- In 1957, a H2N2 reassortant virus emerged with Avian-like HA, NA, and PB1 genes and the remainder human H1N1 genes.
- In 1968, a H3N2 reassortant virus emerged with Avian-like HA and PB1 genes and the remainder human H2N2 genes.

Model 3 of Viral Spread

- Spread through intermediary host.
 - Virus jumps from wild birds to intermediary host.
 - Amplification in intermediary host with some host adaptation.
 - Spread of modified virus to new host.
 - Reassortment between different viruses may play a role.

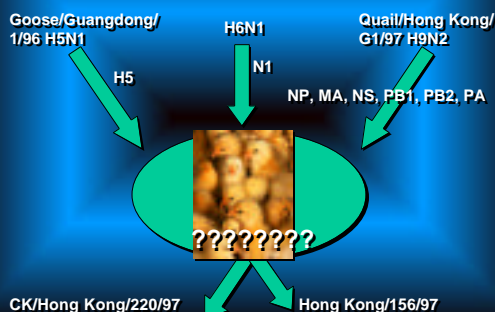
Hong Kong H5N1

- Outbreak of HPAI in poultry, primarily chickens, in live bird markets in Hong Kong.
- Virus was likely reassortant of previously circulating Avian Influenza viruses in poultry.
- Virus spread directly from chickens to humans causing disease with high mortality.

Hong Kong H5N1

- No evidence of person to person spread.
- Eradication of poultry from Hong Kong ended outbreak in humans and poultry.

Origins of Virulent H5N1 Influenza in Hong Kong



Netherlands H7N7

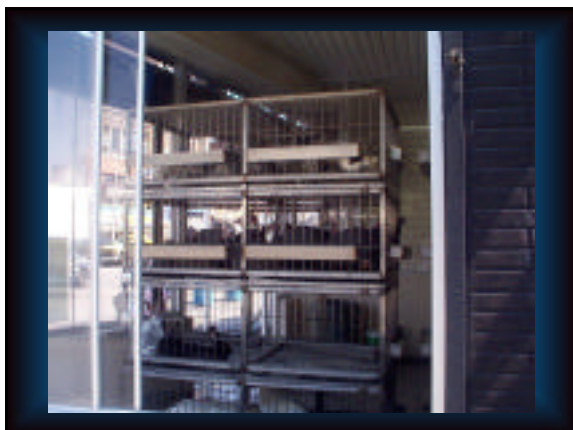
- Outbreak of HPAI in chickens and turkeys, resulting in depopulation of >28 million birds.
- Poultry virus spread to over 80 humans and contributed to one human death.
- Caused mostly conjunctivitis, but some influenza-like illness.
- Some evidence of person to person spread.
- Serologic evidence of H7 infection in pigs on infected poultry farms.

Numbers Game

- Exposure of humans and domestic animals to Avian Influenza viruses occurs frequently.
- Most of the time the viruses don't replicate well because it lacks proper gene constellation.
- Occasionally replicates well (causes disease) but doesn't transmit efficiently.
- Rare opportunities for viruses to adapt and become endemic in new host species.

Initial Introduction of Avian Influenza to Domestic Animals

- Direct interaction of infected wildlife and domestic animals.
 - Common for domestic and wild ducks to mix.
- Exposure to contaminated water source (using unpurified water from surface sources. Ex., lakes, for drinking water).
- Live Bird Markets.



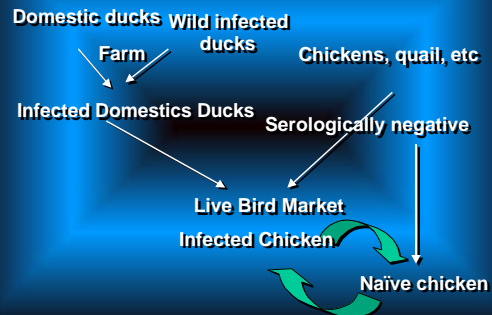
Live Bird Markets (LBMs)

- Provide consumer opportunity to select live birds for consumption.
- Birds are typically killed and dressed at market.
- Primarily chickens sold, but also turkeys, ducks, geese, quail, other gamebirds and mammals.

Live Bird Markets (LBMs)

- LBMs serves a niche of consumers who desire to have or select live birds.
- Consumer pays a premium price for birds compared to poultry at grocery stores.

Risks of Live Bird Markets



How to Prevent Avian Influenza From Infecting Domestic Animals and Humans

- Control of virus in wild birds-not possible.
- Control of exposure of wild birds to domestic animals.
 - Minnesota has reduced Avian Influenza outbreaks in turkeys with change to confinement rearing.

How to Prevent Avian Influenza From Infecting Domestic Animals and Humans

- Chlorination of drinking water from surface sources.
- Separate waterfowl from other poultry in LBMs and mandatory rest days at markets (measures implemented in Hong Kong).

Conclusions

- We remain unable to predict which AI viruses pose a zoonotic risk.
- Exposure to Avian Influenza viruses occurs frequently.
- Few markers for human infection or virulence have been identified (Position 627 of PB2 gene).
- Current animal husbandry practices, particularly live bird markets, provide opportunities for human exposure.
- Minimum levels of precaution should be used with any influenza virus.

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